General

Guideline Title

Optimal chemotherapy for recurrent ovarian cancer.

Bibliographic Source(s)

Fung Kee Fung M, Kennedy E, Francis J, Mackay H, Gynecologic Cancer Disease Site Group. Optimal chemotherapy for recurrent ovarian cancer. Toronto (ON): Cancer Care Ontario (CCO); 2011 Nov 21. Various p. (Evidence-based series; no. 4-3). [89 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Fung Kee Fung M, Johnston M, Eisenhauer E, Elit L, Hirte H, Rosen R and the Gynecological Cancer Disease Site Group. Chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum. Toronto (ON): Cancer Care Ontario (CCO); 2001 Sep 21. (Evidence Summary Report No. 4-3).

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

On the basis of the available data from Phase III randomized controlled trials (RCTs), combined with expert opinion, the Gynecologic Cancer Disease Site Group recommends that:

- Systemic therapy for recurrent ovarian cancer is not curative. As such, it is recognized that, to determine the optimal therapy, each patient needs to be assessed individually in terms of recurrence, sensitivity to platinum, toxicity, ease of administration, and patient preference.
- All patients should be offered the opportunity to participate in clinical trials, if appropriate.
- For patients with prior sensitivity to platinum-containing chemotherapy:
  - All suitable patients should be offered the opportunity to participate in RCTs, if appropriate.
  - If the option to participate in an RCT is not available, combination platinum-based chemotherapy should be considered, providing that there are no contraindications. The decision regarding which combination to use should be based on the considerations listed in the first bullet point above, including toxicity experienced with primary therapy, patient preference, and other factors. Recommended

combinations are:
    - Carboplatin and paclitaxel (C-P)
    - Carboplatin and gemcitabine
    - Carboplatin and pegylated liposomal doxorubicin (C-PLD)
  - If combination platinum-based chemotherapy is contraindicated, then a single platinum agent should be considered. Carboplatin has demonstrated efficacy across trials and has a manageable toxicity profile.
  - If a single platinum agent is not being considered (e.g., because of toxicity), then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.
- For patients with platinum-refractory or platinum-resistant disease:
  - Lower levels of response to treatment are expected for this group; therefore, the goals of treatment should be to improve quality of life (QOL) by extending the symptom-free interval, reducing symptom intensity, increasing progression free interval, or if possible, prolonging life.
  - All suitable patients should be offered the opportunity to participate in clinical trials, if appropriate.
  - Monotherapy with a non-platinum agent should be considered since there does not appear to be an advantage in the use of non-platinum-containing combination chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, pegylated liposomal doxorubicin, and gemcitabine have demonstrated activity in this patient population and are reasonable treatment options.
  - There is no evidence to support or refute the use of more than one line of chemotherapy in patients with platinum-refractory or platinum-resistant recurrences. There are many treatment options that have shown modest response rates but their benefit over best supportive care has not been studied in clinical trials.

Modifications from 2006 Recommendations

The recommendations listed above are predominantly unchanged from the 2006 version of this guideline, with the exception of the addition of C-PLD as a treatment option for platinum-sensitive recurrent ovarian cancer, the addition of single-agent gemcitabine as a treatment option for platinum-resistant ovarian cancer, and the clarification of the recommendation for participation in clinical trials.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Recurrent epithelial ovarian cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Surgery

Intended Users

Physicians

Guideline Objective(s)

To evaluate what is the optimal chemotherapy treatment for women with recurrent ovarian cancer who have previously received platinum-based chemotherapy

Target Population

Women with recurrent epithelial ovarian cancer who have previously received platinum-based chemotherapy

Interventions and Practices Considered

1. Individual assessment
2. Combination chemotherapy
    - Carboplatin and paclitaxel (C-P)
    - Carboplatin and gemcitabine
    - Carboplatin and pegylated liposomal doxorubicin (C-PLD)
3. Single agent chemotherapy
    - Carboplatin
    - Paclitaxel
    - Topotecan
    - Pegylated liposomal doxorubicin
    - Gemcitabine

Major Outcomes Considered

- Progression-free survival (PFS)
- Overall survival (OS)
- Adverse events
- Quality of life (QOL)
- Tumour response rates

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The literature was searched using MEDLINE and EMBASE (OVID: 2006 through March 2011), the Cochrane Library (OVID: Cochrane Central Register of Controlled Trials 1st Quarter 2011, Cochrane Database of Systematic Reviews 2005 to March 2011), the Canadian Medical Association Infobase, and the National Guideline Clearinghouse. In addition, the abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2005-2011) and the European Society for Medical Oncology (2006, 2008, 2010) were searched for

evidence relevant to this report. Reference lists of related papers and recent review articles were also scanned for additional citations.

The literature search of the electronic databases was adopted from the previous version of the guideline and combined the terms (ovarian neoplasms/ or ovarian.ti. and neoplasm:.mp. or cancer.mp.) with (neoplasm recurrence local/ or neoplasm metastasis/ or recurrent:.mp. or relapse:.mp. or resistance.mp.) and (drug therapy/ or antineoplastic agents/ or chemotherapy.mp.) for the following study designs: randomized controlled trials, meta-analyses, practice guidelines, and systematic reviews.

The review also included a search for results from the trials in progress when the previous version of this guideline was published: the Southwest Oncology Group Protocol (SWOG) S0200, Carboplatin-Paclitaxel (C-P) Versus Carboplatin-Pegylated Liposomal Doxorubicin (C-PLD) In Platinum-Sensitive Patients (CALYPSO), and International Collaboration for Ovarian Neoplasia 6 (ICON6).

Inclusion Criteria

Articles were selected for inclusion in the systematic review if they were phase III randomized controlled trials that compared chemotherapeutic agents as part of second or greater line treatment for patients with recurrent epithelial ovarian cancer who were previously treated with platinum-containing chemotherapy. Trials were to report data on at least one of the following outcomes of interest: overall survival (OS), progression-free survival (PFS), adverse events, or quality of life (QOL). Tumour response rate was also considered an outcome of interest. Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion.

Exclusion Criteria

Articles were excluded from the systematic review if they were reported in a language other than English, or if they included the use of intraperitoneal chemotherapy, hormonal therapy, or chemotherapy with bone marrow or stem cell transplantation. Abstracts reporting analyses that were conducted before predetermined trial endpoints were reached were also excluded.

Number of Source Documents

The literature search conducted in 2011 identified six phase III randomized trials comparing various chemotherapy regimens for women with recurrent ovarian cancer.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Methodological Quality Appraisal of Randomized Controlled Trials

Randomized trials that met the inclusion criteria were assessed using information provided in the trial reports: randomization sequence generation, allocation concealment, blinding, analysis details including intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, and differences in baseline patient characteristics.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-Based Series (EBS) guidelines developed by the Program in Evidence-Based Care (PEBC), Cancer Care Ontario, use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. The initial evidence review was conducted by a PEBC methodologist and the studies identified for inclusion were reviewed by the remaining members of the Working Group.

The systematic review is a convenient and up-to-date source of the best available evidence on chemotherapy for the treatment of women with recurrent epithelial ovarian cancer. The body of evidence in this review is comprised of data from phase III randomized controlled trials. That evidence forms the basis of the recommendations found in Section 1 of this EBS.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP) Review and Approval

Prior to the submission of this Evidence-Based Series (EBS) draft report for External Review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) RAP, a panel that includes oncologists and whose members have clinical and methodological expertise.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base in the original guideline document of this EBS and the review and approval of the report by the PEBC RAP, the working group circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, two targeted peer reviewers from Ontario and one from British Columbia, considered to be clinical and/or methodological experts on the topic, were identified by the Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 28, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals in Ontario who are the intended users of the guideline. All individuals in the PEBC database who were identified as having an interest in gynecology and radiation or surgery or systemic treatment were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). A paper copy was also delivered to each person. The notification email was sent on September 28, 2011. The consultation period ended on November 11, 2011. The Working Group reviewed the results of the survey.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process, with final approval given by the Gynecologic Cancer Disease Site Group and the RAP of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Patients with Platinum-sensitive Ovarian Cancer

A 976 patient study, Carboplatin-Pegylated Liposomal Doxorubicin (C-PLD) In Platinum-Sensitive Patients (CALYPSO), compared carboplatin-paclitaxel (C-P) to C-PLD and found an improvement in progression-free survival (PFS) with the PLD combination (11.4 versus [vs.] 9.3 months, p=0.005), a more favourable toxicity profile, no difference in overall survival (OS) (although significantly more patients crossed over to the C-PLD arm), and a superior crossover treatment rate in the C-P arm. Global quality of life (QOL) scores did not differ between groups.

A Mix of Platinum-sensitive and Platinum-resistant Patients

- A 672 patient study, OVA-301, compared PLD to trabectedin-PLD, and found a statistically significantly improved PFS with the combination (7.3 vs. 5.8 months, p=0.019). Despite this finding, which implies the viability of the combination as a treatment option, the trabectedin-PLD combination is not recommended at this time, based on the finding of no differences in QOL or OS, the lack of clinical significance of a six-week PFS difference, the lack of comparison with the Gynecologic Cancer Intergroup (GCIG) standard taxane and platinum agent, and the elevated rate of adverse events such as raised liver enzymes, non-fatal congestive heart failure, and neutropenia in the combination group.
- A study by Sehouli et al. of topotecan versus topotecan combined with other agents did not find a benefit with the combination therapy in a population of mainly platinum-sensitive women; thus, topotecan combination therapy is not recommended.
- Two smaller trials that compared PLD with gemcitabine showed no difference in PFS. A small significant difference in OS was found in one trial (56 weeks for PLD vs. 51 weeks for gemcitabine, p=0.048). The adverse events profiles differ for these two agents; therefore, gemcitabine can be considered another option in this patient population, considering patient preference and previous toxicity.

Potential Harms

Adverse Events Associated with Chemotherapy

- As seen in Table 3 in the original guideline document, data on adverse events varied by treatment regimen, and, while there were differences

in reporting, outcomes correlated with known toxicity profiles.

- Ten trials reported statistically significant differences in adverse events by treatment group. On average, severe adverse events, generally haematological, were significantly associated with combination chemotherapy when compared with single-agent chemotherapy. The agents most commonly used were paclitaxel, carboplatin, topotecan, and pegylated liposomal doxorubicin. Adverse events associated with paclitaxel included alopecia (any grade) in 62% to 100% of patients, neurotoxic effects (any grade) in 5% to 42% of patients, severe leukopenia in 4% to 24% of patients, and severe nausea and vomiting in 2% to 6% of patients. Carboplatin was associated with low severe hematological events, typically less than 15% of patients, severe nausea and vomiting in approximately 10% or less of patients, and any grade of alopecia in 2% to 25% of patients. When compared with paclitaxel or pegylated liposomal doxorubicin, topotecan was significantly associated with increased severe haematological toxicities, and some grade of alopecia occurred in 49% and 76% of patients. The adverse events associated with pegylated liposomal doxorubicin included any grade of palmar-plantar erythrodysesthesia (PPE) in approximately one half of patients, and severe PPE occurred in 23% and 16% of patients, respectively. One trial also reported a significant difference in severe stomatitis in patients treated with pegylated liposomal doxorubicin when compared with paclitaxel (10% versus 1%; p=0.03).

Qualifying Statements

Qualifying Statements

- The results presented in an abstract from *A Study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma (OCEANS)*, a randomized, 484-person, double-blinded, placebo-controlled phase III trial of carboplatin and gemcitabine with or without bevacizumab (Bev) in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer showed a significantly longer progression-free survival (PFS) in the Bev arm (8.4 months vs. 12.4 months, $p<0.0001$). While no recommendation for this treatment option is being made at this time, the publication of the full results of this trial is anticipated and may inform future guideline recommendations.
- A recommendation for trabectedin-pegylated liposomal doxorubicin (PLD) for carboplatin and cisplatin allergic patients may be reasonable, however because the PFS benefit with this combination was modest, and there was no overall survival (OS) difference, a recommendation for this combination is not being made at this time.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 Sep 21 (revised 2011 Nov 21)

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Gynecologic Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest Policy, the guideline authors, Gynecologic Cancer Disease Site Group (DSG) members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Fung Kee Fung M, Johnston M, Eisenhauer E, Elit L, Hirte H, Rosen R and the Gynecological Cancer Disease Site Group. Chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum. Toronto (ON): Cancer Care Ontario (CCO); 2001 Sep 21. (Evidence Summary Report No. 4-3).

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Optimal chemotherapy for recurrent ovarian cancer. Summary. Toronto (ON): Cancer Care Ontario; 2011 Nov 21. 8 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.
- Program in Evidence-Based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

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